Attachment A: Dear Healthcare Professional Letter (DHCPL)

XX (Month) 2015

IMPORTANT DRUG WARNING

FDA-Required Risk Evaluation and Mitigation Strategy (REMS)

Dear Healthcare Professional:

The purpose of this letter is to inform you of new important safety information for GILENYA® (fingolimod), based on the May 2015 prescribing information.

GILENYA is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. GILENYA is a sphingosine 1-phosphate receptor (S1P) modulator. GILENYA blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood to approximately 30% of baseline values. The mechanism by which GILENYA exerts therapeutic effects in MS is unknown, but may involve reduction of lymphocyte migration into the central nervous system.

The overall exposure in the controlled trials was equivalent to 1716 person-years. Approximately 1000 patients have received at least 2 years of treatment with GILENYA 0.5 mg. In all clinical studies, including uncontrolled extension studies, the exposure to GILENYA 0.5 mg is approximately 4119 person-years.

Bradyarrhythmia and Atrioventricular (AV) Block

Initiation of GILENYA treatment results in a decrease in heart rate. In controlled studies, GILENYA has also been associated with AV conduction delays, including first or second degree AV block, following initiation of treatment. After the first dose of GILENYA, the heart rate decrease starts within an hour and the Day 1 nadir generally occurs within approximately 6 hours, although the nadir can be observed up to 24 hours after the first dose in some patients. In controlled clinical trials, adverse reactions of symptomatic bradycardia following the first dose were reported in 0.6% of patients receiving GILENYA 0.5 mg, and in 0.1% of patients on placebo. The conduction abnormalities were usually transient and asymptomatic, and resolved within the first 24 hours on treatment, but they occasionally required treatment with atropine or isoproterenol.

Recommendations for first dose monitoring

When beginning treatment with GILENYA:

- All patients should be observed for signs and symptoms of bradycardia for a period of at least 6 hours after the first dose of GILENYA.

- Hourly blood pressure and pulse measurements should be obtained during this timeframe.
- All patients should have an electrocardiogram (ECG) prior to the first dose of GILENYA and after the 6 hour observation period.
- Patients with a heart rate < 45 bpm or new onset 2nd degree or higher AV block at 6 hours postdose or patients registering the lowest postdose heart rate at the end of the observation period should be monitored until resolution of the finding.
- In patients experiencing post dose symptomatic bradycardia, continuous ECG monitoring should be instituted along with initiation of appropriate treatment and observation until the symptoms have resolved; if pharmacological intervention is required to treat symptomatic bradycardia, continuous overnight ECG monitoring in a medical facility should be instituted, and first dose monitoring procedures should be repeated after the second dose of GILENYA.
- Patients at higher risk of symptomatic bradycardia or bradyarrhythmia due to coexisting medical conditions or certain concomitant medications should have a cardiac evaluation by a physician appropriately trained to conduct such evaluation prior to treatment with GILENYA, and, if treated with GILENYA, should be observed overnight in a medical facility with continuous ECG monitoring.
- Patients with prolonged QTc interval at baseline or during the observation period, or at additional risk for QT prolongation or taking drugs with known risk of torsades de pointes should be observed overnight in a medical facility with continuous ECG monitoring.
- Patients receiving concomitant therapies that slow heart rate or AV conduction should be evaluated with possibility of switching off these drugs prior to initiation of GILENYA. Patients who cannot switch should have overnight observation in a medical facility with continuous ECG monitoring.

Reinitiation of therapy following discontinuation

If GILENYA therapy is discontinued for more than 14 days after the first month of treatment, the effects on heart rate and AV conduction may recur on reintroduction of GILENYA treatment and the same precautions (first dose monitoring) as for initial dosing should apply.

The need for first dose monitoring following treatment interruption varies depending on time on GILENYA prior to treatment interruption, as described below:

Length of treatment with GILENYA prior to interruption in therapy	Length of interruption necessitating first dose monitoring (consecutive days of missed doses)
Up to 2 weeks	1 day or more
3 to 4 weeks	7 days or more
More than 1 month	14 days or more

Contraindications

GILENYA is contraindicated in patients

- with recent (within the last 6 months) myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure
- with a history or presence of Mobitz Type II 2nd or 3rd degree AV block or sick sinus syndrome, unless the patient has a functional pacemaker

- with a baseline QTc interval ≥ 500 msec
- receiving treatment with Class Ia or Class III anti-arrhythmic drugs

Infections

GILENYA causes a dose-dependent, reversible sequestration of lymphocytes in lymphoid tissues resulting in a reduction of peripheral blood lymphocyte count to 20% - 30% of baseline values.

- Before initiating treatment with GILENYA, a recent CBC (i.e. within the last 6 months or after discontinuation of prior therapy) should be available.
- Consider suspending treatment with GILENYA if a patient develops a serious infection, and reassess the benefits and risks prior to reinitiation of therapy.
- Serious, life-threatening events of disseminated varicella zoster and herpes simplex infections, including cases of encephalitis and multiorgan failure, have occurred with GILENYA 0.5 mg in the postmarketing setting. One of these events was fatal. Include disseminated herpetic infections in the differential diagnosis of patients who are receiving GILENYA and present with an atypical MS relapse or multiorgan failure.
- Patients without a healthcare professional confirmed history of chickenpox or without documentation of a full course of vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV before initiating GILENYA. VZV vaccination of antibody negative patients is recommended prior to commencing treatment with GILENYA, following which initiation of treatment with GILENYA should be postponed for one month to allow for full effect of vaccination to occur.
- Avoid the use of live attenuated vaccines during and for 2 months after treatment with GILENYA because of the risk of infection.
- When switching to GILENYA from other immune-modulating or immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immunosuppressive effects.

Macular Edema

In 2-year, double-blind, placebo-controlled studies in patients with multiple sclerosis, macular edema with or without visual symptoms occurred in 0.5% of patients treated with GILENYA 0.5 mg and 0.4% of patients treated with placebo. Macular edema occurred predominantly during the first 3 to 4 months of therapy. Routine ophthalmological examination detected macular edema in some patients with no visual symptoms. Macular edema generally partially or completely resolved with or without treatment after drug discontinuation. Some patients had residual visual acuity loss even after resolution of macular edema.

- Perform an examination of the fundus including the macula in all patients before starting treatment, again 3-4 months after treatment initiation, and again any time after a patient reports visual disturbances while on GILENYA therapy.
  Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular edema during GILENYA therapy. In addition to the examination of the fundus including the macula prior to treatment and at 3-4 months after starting treatment, MS patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations.

Posterior Reversible Encephalopathy Syndrome

There have been rare cases of posterior reversible encephalopathy syndrome (PRES) reported in patients receiving GILENYA. Symptoms reported included sudden onset of severe headache, altered mental status, visual disturbances and seizure. Symptoms of PRES are usually reversible, but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, GILENYA should be discontinued.

Respiratory Effects

Small dose-dependent reductions in forced expiratory volume over one second (FEV1) and Diffusion Capacity of the Lung for Carbon Monoxide (DLCO) were observed in patients treated with GILENYA, as early as 1 month after treatment initiation. The changes in FEV1 appear to be reversible after treatment discontinuation. There is insufficient information to determine the reversibility of the decrease of DLCO after drug discontinuation.

- Spirometric evaluation of respiratory function and evaluation of DLCO should be performed during therapy with GILENYA if clinically indicated.

Liver Injury

- Elevations of liver function tests may occur in patients receiving GILENYA. The majority of elevations occurred within 6-9 months.Recent (i.e. within the last 6 months) transaminase and bilirubin levels should be available before initiation of GILENYA therapy.
- Liver enzymes should be monitored in patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. GILENYA should be discontinued if significant liver injury is confirmed. Patients with pre-existing liver disease may be at increased risk of developing elevated liver function tests when taking GILENYA.

Fetal Risk

Based on animal studies, GILENYA may cause fetal harm.

- There are no adequate and well-controlled studies of GILENYA in pregnant women.
- Women of childbearing potential should be counseled on the potential risk to the fetus and advised to use effective contraception during and for at least 2 months following discontinuation of GILENYA therapy.
- Women who become pregnant while on therapy must be counseled on potential risk to the fetus.
- GILENYA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Since there are no adequate and well-controlled studies of GILENYA in pregnant women, a pregnancy registry has been established to collect information about the effects of GILENYA during pregnancy. Physicians are encouraged to register patients who become pregnant while exposed to GILENYA or within 2 months after stopping therapy. Prescribers with an eligible patient, or patients themselves, can contact the Pregnancy Exposure Registry by calling Outcome at 1-877-598-7237, sending an email to gpr@outcome.com or visiting www.gilenyapregnancyregistry.com.

Reporting adverse events

To report all suspected adverse events associated with the use of GILENYA contact:

- Novartis Drug Safety & Epidemiology at 1-888-NOW-NOVA (669-6682)
- FDA at 1-800-FDA-1088 or www.fda.gov/ medwatch.

Please see the accompanying complete updated Prescribing Information and Medication Guide. For more information regarding GILENYA, please contact Novartis Medical Information and Communication at 1-888-NOW-NOVA (669-6682) or visit the website at www.GILENYA.com.

Sincerely,

Cathryn M. Clary, MD
Head, US Clinical Development and Medical Affairs
Novartis Pharmaceuticals Corporation